Rhinology, 36, 188–191, 1998

Wegener's granulomatosis - A review of diagnosis and treatment in 53 subjects*

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SUMMARY

We reviewed 79 patients with clinically suspected Wegener's granulomatosis (WG) diagnosed in Nottingham between 1990 and 1997. Fifty-three patients were confirmed as having WG. We describe the symptoms and signs, features of diagnostic significance, ANCA results, biopsy sites, histology, treatment and outcome in this group. Nasal symptoms and signs had a positive predictive value of 63%, c-ANCA at presentation 100%, and positive nasal biopsy 100%. The negative predictive values were 41%; 79% and 74% respectively. From this study, we recommend that patients who have a negative ANCA and where there remains a clinical suspicion of WG, an ENT examination should be undertaken. Whilst a suspicious lesion should be biopsied and a positive histological picture has a 100% positive predictive value, a negative nasal biopsy does not exclude WG as 5 patients went on to develop a positive ANCA up to 4 years later. In 11 ANCA negative patients where there were signs of nasal mucosal disease, 6 had a positive biopsy and this highlights the importance of nasal biopsy. The c-ANCA should be repeated in patients with a negative c-ANCA and biopsy results at presentation, in whom there remains a clinical suspicion of WG.

Key words: Granulomatosis, Vasculitis, Wegener's Granulomatosis, Nasal.

INTRODUCTION

Wegener's granulomatosis (WG) is a form of necrotising vasculitis affecting the small arteries of the upper and lower respiratory tracts and kidney though it may involve any organ system. The first case was described in 1931 by Klinger (Klinger 1931). Wegener described an identical case in 1936, and went on to write up a series in 1939 (Wegener 1939). The aetiology of the condition is unknown. The diagnosis of Wegener's granulomatosis depends on the clinical features, the biopsy result of related lesions, and positive cytoplasmic antineutrophil cytoplasmic antibody titres (c-ANCA). A positive ANCA and suggestive biopsy, are sensitive tests for WG and are considered to be of equal importance (De Remee 1994). Clinical features alone are not sensitive.

Wegener's granulomatosis is a systemic disease, though most patients present with localised expression (Murty 1990). Systems most commonly affected are the upper and lower respiratory tracts and the kidney. Workers at the Mayo clinic have attempted to stage WG according to the clinical presentation (DeRemee 1976), with upper respiratory symptoms being denoted by E, lung by L, and kidney by K, with combinations being expressed, in a patient with all three symptom sites would be staged as ELK. The prognosis was best in E stage patients and worse with combinations of L or K. Interestingly K lesions alone were not classified as WG, until the antineutrophil cytoplasmic antibody test (ANCA) in 1985 (van der Woude 1985) was found to add considerable diagnostic support (De Remee 1994). The biopsy of a Wegener's lesion has the following features as identified first by Wegener (Wegener 1939) and set out by Saldaman in 1977 (Saldaman 1977): All biopsies show an inflammatory exudate rich in polymorphonuclear leucocytes with variable features of:

1. small artery vasculitis
2. histiocytic giant cells
3. epithelioid cell granulomas Rasmussen et al (Rasmussen 1990) used these features to rate the probahility of a lesion being due to WG.
   - Typical Wegener's has all 3 features
   - Lesions compatible with WG have 2 out of 3
   - Non specific inflammatory lesions have 1 out of 3
   - Normal tissue has none.

The commonest histological finding in lesions from patients with WG is small vessel vasculitis alone (Rasmussen 1990). The c-ANCA was found to be strongly associated with WG by van der Woude in 1985 (van der Woude 1985). The Antiproteinase 3 antibodies be ELISA react with a 27 kd neutral serine protei-

* Received for publication May 19, 1998; accepted July 8, 1998

nase called proteinase 3 which is found in the primary granules of the cytoplasm of neutrophils and monocytes (Ludemann 1990). The c-ANCA assay has a 92% sensitivity and a 96% specificity for the diagnosis of WG (Kerr 1993).

The aim of the study was to review all patients with WG in Nottingham diagnosed from 1990 to 1997 to ascertain in each case how the diagnosis was reached and to determine those features of diagnostic significance. Our hypothesis was that patients with no signs in the upper airways may still have local active disease which might be revealed as a nasal biopsy. The presenting symptoms and signs, treatment outcome, the biopsy sites and reports, and the ANCA result were recorded in each patient.

METHOD

Seventy-nine patients were seen in whom a diagnosis of WG was clinically suspected between 1990 and 1997. These patients records were examined retrospectively and were traced using a database of patients from clinical immunology and rhinology clinics, and also a search of patients whose pathology report identified WG. The presenting symptoms and findings were collated, with particular reference to the ENT symptoms. The results of ANCA and biopsies were also reviewed to see which contributed most to the diagnosis. Finally the outcome of treatment was noted. Fifty-three patients had a diagnosis of WG whilst 26 were seen in whom the diagnosis although suspected subsequently proved not to have WG. In the latter group of 26 patients, 10 had nasal symptoms and signs consistent with WG, but none of these individuals had a positive biopsy or positive ANCA test after at least one year of follow-up.

RESULTS

Of the 53 patients reviewed with diagnosed WG, 36 were male and 17 female. The age range at presentation was 26 to 79 years (mean age 55). Four cases were not included in the analysis as only part of their notes could be found and these contained sparse clinical date. The symptoms are presented in Figure 1.

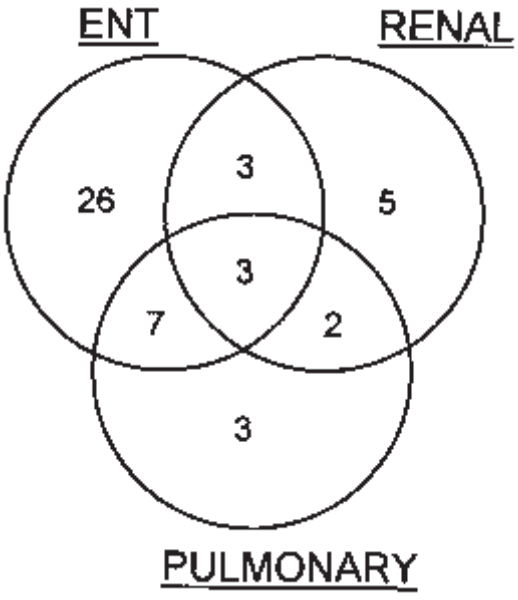

Figure 1. Venn Diagram of Patient Svmptoms and Signs

Thirty-nine (80%) of the 49 patients had disease affecting the ear, nose or throat, 13 (27%) renal involvement and 15 (31%) had pulmonary involvement. Twenty-six of the patients had ophthalmic symptoms, and 21 patients had musculoskeletal symptoms including arthralgia, myalgia and muscle weakness. Five patients were diagnosed as having Wegener's granulomatosis with pulmonary, renal or ENT symptoms, and the diagnosis was made on the basis of a positive ANCA or biopsy result. These 5 patients consisted of 3 with ophthalmic symptoms alone and two with only arthralgia.

Table 1. ENT Symptoms and Signs.

Rhinological (n=27)		Otological (n= 12)		Laryngeal (n=5)	
Blockage	5	Effusion	6	Hoarseness	5
Epistaxis	6	Tinnitus	4	Subglottic Stenosis	2
Crusting	8	Hearing Loss	8		
Hyposmia	2	Middle Ear Polyp	2		
Discharge	9				
Polyps	3				
Septal Ulcer	4				
Septal Perforation	3				
Mass in nose	2				
Erosion lateral nasal wall	2				
Epiphora	2				

The ENT features were primarily nasal. The commonest symptoms were discharge, crusting and epistaxis (see Table 1). Common ENT signs included granular mucosa, crusting, and septal perforation (see Figures 2 and 3). Eight had ENT symptoms and had not been referred for ENT clinical appraisal.

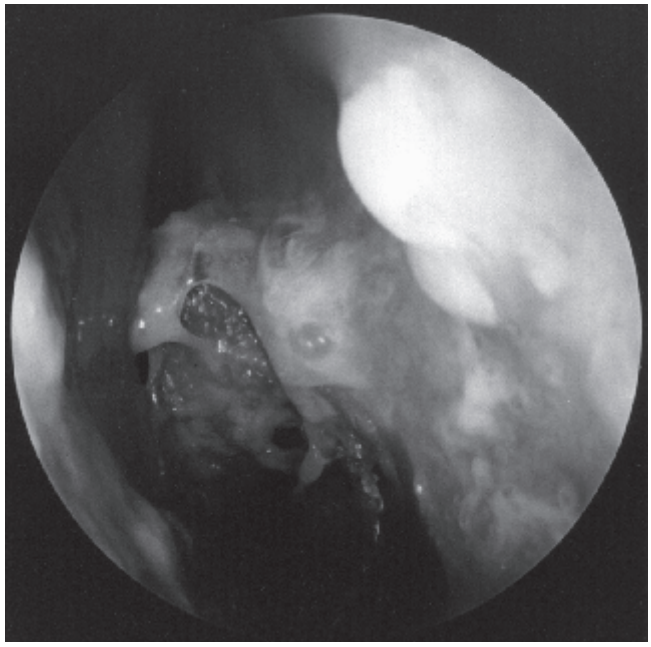

Figure 2. Crusting and Granulomatous Nasal Mucosa.

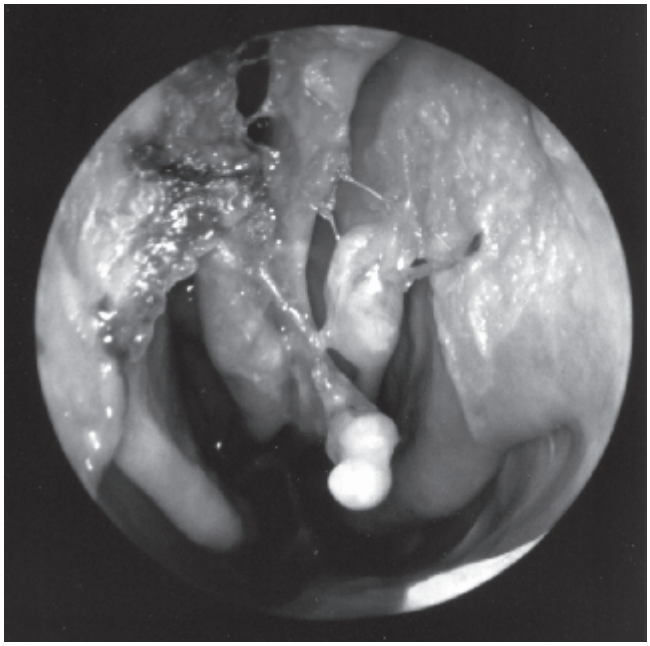

Figure 3. Septal Perforation Secondary to Wegener's Granulomatosis.

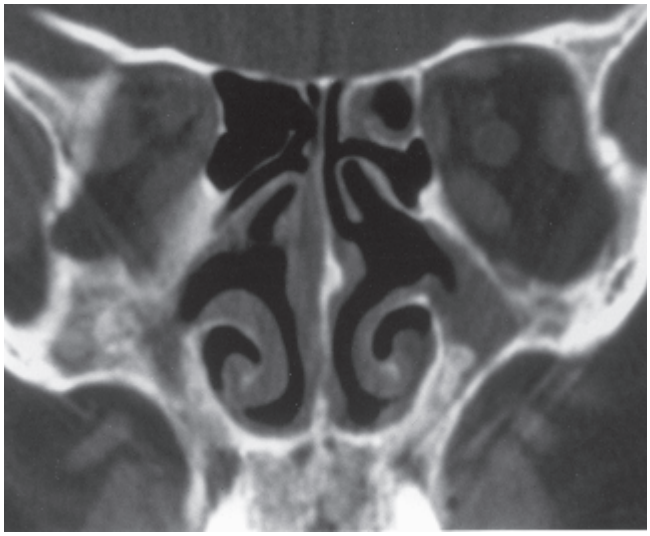

Figure 4. CT Scan of Erosion of the Middle Meatus.

BIOPSY RESULTS

Forty-five patients had biopsy results of whom 32 had histiological features typical or compatible with WG. The wording of the reports differed between pathologists, however most commented only on the presence of vaculitis. ENT biopsies were taken from the larynx (n=l) which was negative and from the nose (n=19). Nineteen nasal biopsies were taken, 10 were positive or compatible, 9 were negative. All these with positive biopsies had signs of mucosal disease. Three of those with negative biopsies had no symptoms or signs. The other 6 negative biopsies were from patients with visible nasal pathology, 3 were from septal perforations, 2 from granular mucosa and 1 from a septal ulcer.

Care was taken to provide a wedge of tissue from the edge of the septal perforations which included normal tissue and did not limit the biopsy to a small piece of necrotic slough. No biopsies were taken from middle ear mucosa (see Table 2).

Table 2. Histological Results of Other Biopsy Sites.

Site	Positive or suggestive		Total
Nose	10	(53%)	19
Kidney	11	(79%)	14
Orbit	4	(100%)	4
Lung	3	(100%)	3
Muscle	2	(100%)	2
Skin	1	(100%)	1
Larynx	0	(0%)	1

In the 26 patients with no eventual diagnosis of WG all had a nasal biopsy, 10 from an area that on inspection appeared inflamed, and 16 had a random biopsy of normal mucosa. None showed any evidence of a vasculitic process.

ANCA RESULTS

Forty-seven patients of those who proved to have WG had a c-ANCA test recorded. Six had no test result. Eleven patients were c-ANCA negative at presentation. Six of these patients had a compatible biopsy leading to an early diagnosis of WG. The remaining five were followed up with repeat c-ANCA assays which became positive from 3 months to 4 years after presentation. Four of these had symptoms confined to the eye, and 1 to the lung. None of the 26 who proved not to have WG were c-ANCA positive.

Table 3. Predictive Values of Parameters Studied.

Predictive factor	Positive predictive value	Negative predictive value
Nasal symptoms and signs	27/27+16 = 63%	16/23+16 = 41%
ANCA result at presentation	36/36 = 100%	26/26 + 11 = 79% After 4 years 26/26 + 6 = 81%
Nasal biopsy result	10/10 = 100%	26/9 + 26 = 74%

OUTCOMES

The treatment of 49 patients with proven WG were available for review. The commonest treatment was a combination of pulse cyclophosphamide starting at 1000 mg four times a week, and prednisolone at a starting dose of 1000 mg weekly, 40 patients had this regime alone. Four patients had azthioprine added as part of their treatment, 4 were treated with prednisolone on its own, and 1 had self limiting disease that has not required active treatment yet. The ANCA titres of 17 patients reduced as a result of treatment. Of these 14 became negative and 3 titres fell but were still positive.

In 6 patients the ANCA was unchanged, i.e. remaining positive. In 21 patients no repeat ANCA was performed. The activity of the disease was monitored on the basis of symptoms, erythrocyte sedimentation rtate and indicators of renal and respiratory function, and not ANCA titres. In 44 patients disease remission was achieved but there were 5 deaths. Two died of renal failure

due to uncontrolled WG, and 2 patients died of opportunistic Pneumocystis carinii pneumonia secondary to the immunosuppression. One patient died following a myocardial infarction, which was not thought to be related to WG or its treatment.

DISCUSSION

ENT symptoms were the commonest presenting features for Wegener's granulomatosis in our series. The pathognomonic renal and lung manifestations were less common than those from the orbit or musculoskeletal systems, each of which accounted for approximately 50% of the patient group. This contrasts with a large prospective study of 158 patients followed up from 6 months to 24 years by Hoffman et al. (Hoffman 1992) who found 85% had lung and 77% had renal pathology, though he did identify a significant proportion with orbital and musculoskeletal disease. One might speculate that the reason for this difference is that since the ANCA assay became widely available in the mid-1980's, the serological investigation of WG has facilitated the early identification of cases. Treatment can be instituted earlier, then by avoiding the progression of disease to involve the lung and kidney. Upper airway involvement is the commonest site of onset for WG and hence it is recommended that in ANCA negative patients where there is a suspicion of Wegener's granulomatosis they should be referred for an ear, nose and throat examination.

ANCA tests are sensitive and specific for WG. Few conditions other than WG give a positive c-ANCA result (Kerr 1993). In some patients the ANCA titres may be negative at presentation, these are usually patients with localised disease. We recommend that those with a negative biopsy and a negative ANCA but with a suspicion of WG should have their ANCA repeated for up to 4 years or possibly longer. In this series 5 patients with a negative ANCA presentation became positive up to 4 years later.

In most cases biopsy of suspicious lesions provided a sensitive and specific method of diagnosing WG. Surprisingly the highest false negative rate of biopsy was in the nose, where access and endoscopic view would be optimal. In 6 of our patients biopsy of quite substantial lesions, such as a septal perforation or septal ulcer sometimes did not show histology suggestive of WG in patients who had disease. This could be explained by the disease being quiescent, the biopsy being too small and unrepresentative, or the nasal finding not being related to the WG. Random biopsy of nasal mucosa with a normal appearance in our cohort of patients was unrewarding but there were only 3 patients in this category. We found a positive nasal biopsy to have a positive predictive value of 100%, indicating no false positive results. The negative predictive value was 74% reflecting a significant number of false negative results. It is important that a biopsy is taken as for a neoplasm so that it includes macroscopically normal mucosa as well as abnormal tissue. A biopsy which is restricted to the edge of a septal perforation is likely to contain necrotic slough which is likely to be unhelpful. The treatment of WG patients was successful in 90% of cases who achieved remission. In our series 5 (10%) of patients died. This is less than Hoffman's study (Hoffman 1992) of 20% WG related deaths, this difference may be related to a longer follow up period. In this study there were no patients treated with long term low dose co-trimoxazole to prevent relapse.

CONCLUSION

1. Patients with suspected WG and a negative ANCA should have a full ENT examination.
2. In ANCA negative patients a biopsy of any granular or inflamed mucosal lesion may help to make the diagnosis of WG. This may not be a very sensitive test, however a positive result has a very high predictive value. The importance of nasal biopsy is illustrated in this series by 6 patients who were ANCA negative and in whom a biopsy established the diagnosis.
3. A negative nasal biopsy, even of a florid lesion, does not exclude WG.
4. ANCA assays should be repeated in patients with persisting clinical features that suggest WG, and who have had a negative ANCA and biopsy at presentation. This is illustrated in our series by 5 patients who became ANCA positive up to 4 years after presentation.

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